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09/837,806	04/18/2001	Sudhir Agrawal	HYZ-069CN (47508-407)	8489

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EXAMINER
ZARA, JANE J

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1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/837,806	Applicant(s) AGRAWAL, SUDHIR	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-39 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-39 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7, 10, 11, 17-22, 25, 26, 32, 33, 35, 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2 and 17, lines 2-5 for claim 2 and lines 2-6 for claim 17, the distinction between comprising "at least two 3' terminal ribonucleotides, at least two 5'-terminal ribonucleotides, or at least two 3'-terminal and at least two 5' terminal ribonucleotides" is vague and unclear. Clarification is requested.

In claims 6 and 21, lines 2-5, the phrase "consist essentially of four 3'-terminal ribonucleotides and four 3'-terminal ribonucleotides, flanking 13 deoxynucleotides" is vague and unclear. Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-30, 34-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro administration of an antisense oligonucleotide consisting of 21 nucleotides which specifically targets nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5, whereby HIV-1 infection is decreased, does not reasonably provide enablement for the inhibition or treatment of HIV-1 or HIV-2 infection in an organism comprising the administration of these antisense oligonucleotides, nor is enablement provided for a method of introducing an intact oligonucleotide into a mammal comprising the oral administration of the oligonucleotide, which oligonucleotides does not contain 2' - modifications such as 2'-O-methyl groups on its termini. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of treating and inhibiting HIV-1 and HIV-2 infection in an organism comprising the administration of an antisense oligonucleotide consisting of 21 nucleotides which specifically targets nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5, which antisense oligonucleotide optionally further comprises at least two 3' and/or at least two 5'-terminal ribonucleotides, comprises 2'-substituted ribonucleotides such as 2'-O-methyl ribonucleotides, and further comprises phosphorothioate internucleotide linkages. The claims are also drawn to a method of introducing an intact oligonucleotide into a mammal comprising the oral administration of an antisense oligonucleotide consisting of 21 nucleotides which specifically targets nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID

NO: 5, and which oligonucleotide comprises phorothioate internucleotide linkages and terminal ribonucleotides at the 5' and/or 3' termini, but does not contain 5' or 3' terminal 2'-O-modifications..

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80).

Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the

specification toward a method of treating or inhibiting HIV-1 or HIV-2 infections, or inhibiting HIV-1 or HIV-2 proliferation in an organism comprising the administration of antisense oligonucleotides 21 bases in length which specifically target nucleotides 324-345 of SEQ ID NO: 5, nor optionally comprising 2'-O-modifications, 5'-/3'-terminal ribonucleotides nor phosphorothioate internucleotide linkages. Applicants have not provided guidance in the specification toward a method of administering intact antisense oligonucleotides 21 bases in length which specifically target nucleotides 324-345 of SEQ ID NO: 5 via oral administration to an organism, whereby the oligonucletides are present in intact form in the systemic plasma following oral administration to the organism, which oligonucleotides do not contain 3' or 5' terminal 2'-O-modifications.

The specification teaches the inhibition of HIV-1 infection in HIV infected (using various HIV strains for infection) human monocyte-macrophages (or MT-4 cells) in vitro comprising the administration of antisense oligonucleotides 21 bases in length which specifically target nucleotides 324-345 of SEQ ID NO: 5. The specification also teaches protocols for testing the stability of antisense oligonucleotides in an organism following oral administration of radioactively labeled oligonucleotides. The specification fails to teach the treatment, inhibition of infection of HIV-1 or HIV-2 in an organism, or the prevention of HIV-1 or HIV-2 proliferation in an organism comprising the administration of the claimed antisense oligonucleotides. The specification fails to teach the presence of intact oligonucleotides in the systemic plasma of animals following oral administration of antisense oligonucleotides, which oligonucleotides do

not contain 5' or 3' terminal 2'-O-modifications. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of expression of nucleic acids encoding gag of HIV-1 or the in vitro inhibition of HIV-1 infection following administration of antisense oligonucleotides to cells in culture as being correlative or representative of the successful treatment and inhibition of infection of HIV-1 or HIV-2 in an organism and the successful inhibition of HIV-1 or HIV-2 proliferation in an organism in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of antisense in treating HIV-1 or HIV-2 infections, or in inhibiting HIV-1 or HIV-2 infections or inhibiting the proliferation of HIV-1 or HIV-2 in an organism comprising the administration of antisense oligonucleotides. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of treating and inhibiting HIV-1 and HIV-2 infection in an organism comprising the administration of an antisense oligonucleotide consisting of 21 nucleotides which specifically targets nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5, which antisense oligonculeotide optionally further comprises least two 3' and/or at least two 5'-terminal ribonucleotides, comprises 2'-substituted ribonucleotides such as 2'-O-methyl ribonucleotides, and phosphorothioate

internucleotide linkages. The claims are also drawn to a method of introducing an intact oligonucleotide into a mammal comprising the oral administration of an antisense oligonucleotide consisting of 21 nucleotides which specifically targets nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5, which antisense does not contain 3' or 5' terminal 2'-O modifications, but comprise phosphorothioate internucleotide linkages and optionally comprise ribonucleotides and futher optionally comprise 2'-O-modifications on its 3' and/or 5' termini. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring HIV-1 or HIV-2, or cells which are susceptible to infection by HIV-1 or HIV-2, whereby viral infection, replication and proliferation is inhibited in vivo, and further whereby treatment effects are provided. The de novo determination of the in vivo stability following oral administration of antisense oligonucleotides which do not contain 5' or 3' terminal 2'-O-modified nucleotides is also required to enable the scope claimed. Since the specification fails to provide any particular guidance for the successful inhibition of HIV-1 or HIV-2 infection in vivo, nor for the successful treatment of HIV-1 or HIV-2 infections in an organism, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 39 is directed to the same invention as that of claim 1 of commonly assigned patent, USPN 5,591,721. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al, in view of Goodchild et al and Hovanessian et al insofar as the claims are drawn to compositions and methods for inhibiting HIV-1 and HIV-2 infection in vitro comprising the administration of antisense oligonucleotides consisting of 21 nucleotides which specifically target nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5, including SEQ ID Nos: 1-4, which oligonucleotides comprise phosphorothioate internucleotide linkages, optionally comprise at least two 5' and 3' terminal ribonucleotides which optionally comprise 2'-O-modifications, and which compositions comprise a pharmaceutically acceptable carrier.

Agrawal et al (USPN 5,591,721) teach methods and compositions for inhibiting HIV infections in vitro comprising the administration of antisense oligonucleotides between 15 and 25 nucleobases in length which specifically target nucleotides 324-345 of gag of the HIV-1 genome

set forth as SEQ ID NO: 5, including SEQ ID Nos: 1-4, which oligonucleotides comprise phosphorothioate internucleotide linkages, optionally comprise at least two 5' and 3' terminal ribonucleotides which optionally comprise 2'-O-modifications, and which compositions comprise a pharmaceutically acceptable carrier (See entire text, especially the abstract, columns 1-4, columns 6-9, SEQ ID NO: 1, claim 1).

Agrawal et al do not teach the antisense oligonucleotides consisting of SEQ ID Nos: 1-4, which are 21 nucleobases in length and specifically target nucleotides 324-345 of gag of the HIV-1 genome set forth as SEQ ID NO: 5. Agrawal et al do not teach assays for the detection of HIV-2 infections in vitro.

Goodchild et al teach compositions and methods for inhibiting HIV infections in vitro using antisense oligonucleotides (see especially columns 4-6, example 3 in columns 10-13).

Hovanessian et al teach compositions and methods for detecting HIV infections in vitro, including HIV-1 and HIV-2. Hovanessian et al also teach the similarities and differences between HIV-1 and HIV-2 nucleic acids encoding HIV proteins and polypeptides (see especially columns 1-4 and column 7).

It would have been obvious to one of ordinary skill in the art to utilize antisense oligonucleotides of 21 nucleobases in length, and which sequences (i.e. of SEQ ID Nos: 1-4 of the instant invention) are **embedded within** the previously disclosed SEQ ID NO: 1 of USPN 5,591,721, to target the gag HIV-1 gene in vitro in order to inhibit HIV infection in vitro, including HIV-1 and HIV-2 infections, because this larger antisense oligonucleotide of 25

nucleobases had been disclosed previously by Agrawal et al for targeting the gag gene in order to inhibit HIV infections in vitro, and it would have been obvious to utilize smaller sequences within this larger 25 nucleobase sequence, and between 15 and 25 nucleobases in length, to inhibit the target gag gene expression in vitro, because this oligonucleotide range (15 to 25 nucleobase lengths) was found an optimal range for cellular uptake, target gene binding and inhibition of target gene expression, as taught previously by Agrawal et al. One of ordinary skill in the art would have been motivated to utilize smaller, embedded sequences within the previously disclosed 25 nucleobase antisense because it was known in the art at the time of the invention that smaller oligonucleotides have enhanced cellular uptake and enhanced target binding than larger oligonucleotides, furthermore, smaller oligonucleotides would be more economically efficient to synthesize than the 25 nucleobase oligonucleotide previously disclosed by Agrawal et al, and the techniques for testing antisense oligonucleotides for inhibiting viral infections, including for HIV-1 and HIV-2 infections in cells in vitro were routine in the art, as taught previously by Goodchild et al and Hovanessian et al. One of ordinary skill in the art would have expected that the in vitro inhibition of gag expression by antisense, including the instantly claimed antisense of lengths of 21 nucleobases would lead to the in vitro inhibition of HIV-1 and HIV-2 replication in vitro, because the success of antisense inhibition of HIV in vitro had been demonstrated previously by Goodchild et al and the similarities between HIV-1 and HIV-2 nucleic acids encoding the various viral proteins had been taught previously by Hovanessian et al. One of ordinary skill in the art would have been motivated to incorporate

phosphorothioate internucleotide linkages, ribonucleotides at the 5' and 3' termini, and 2'-O-modifications within the ribonucleotides at the 5' and 3' termini of antisense oligonucleotides, including at the 5' and 3' termini and in at least 2 residues per termini, because it had been taught previously by Agrawal et al that the incorporation of such modifications into ribonucleotide termini enhance the stability of antisense oligonucleotides from nuclease degradation. One of ordinary skill in the art would have expected that antisense oligonucleotides comprising these modifications would provide enhanced target gene inhibition because of their enhanced stability, and because it had been known in the art that such modifications as phorphorothioate internucleotide linkages enhances target binding and cellular uptake of oligonucleotides.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC 1600

JZ

August 26, 2002